UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,009	12/02/2003	Andrew Geall	1530.0620001/EKS/J-H	3175

26111 7590 05/17/2007

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
05/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,009	GEALL, ANDREW	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendments

1. The amendments filed February 23, have been entered. Claim 1 has been amended. Claims 29-45 have been newly added. Claims 1-45 are under consideration in this office action.

Response to Arguments

2. Applicant's arguments with respect to claims 1-45 have been considered but are moot in view of the new grounds of rejection. Applicant's amendment necessitated the new grounds of rejection presented in this Office Action.

New Grounds of Rejection Necessitated by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 is drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer;

(ii) a polynucleotide; (iii) a cationic surfactant; and (iv) a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture.

Neither the specification nor originally presented claims provides support for a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof. Applicant did not point to support in the specification for a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof. Moreover, applicant failed to specifically point to the identity or provide structural characteristics of the compound selected from the group consisting of mixtures thereof. Applicant has pointed to paragraphs [0082] and [0086] of the instant specification and claims for support of the amendment, however it appears that paragraphs [0082] and [0086] and the entire specification fail to recite support for the newly recited method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures thereof. At best, there is support for a single compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, and proteins. Thus, the specification fails to disclose a mixture of compounds. Therefore, it appears that there is no support in the specification. Therefore, applicants must specifically point to page and line number support for the identity a method of preparing a lyophilized composition or a composition comprising a compound selected from the group consisting of mixtures

thereof as recited by the amended claim. Therefore, amendment claim 1 incorporates new matter and is accordingly rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites the limitation "said amorphous cryoprotectant or crystalline bulking agent" in the claim or its parent claim. There is insufficient antecedent basis for this limitation in the claim. It is unclear as to what agent the claim refers to. Therefore clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-2, 5, 8-13, 15-24, 27-32, 37-39 and 40-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans (WO 02/00844) in view of Volkin et al., (WO 97/408839).

Claim 1 is drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer;

(ii) a polynucleotide; (iii) a cationic surfactant; and (iv) a monosaccharide, disaccharide or oligosaccharide compound; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture. Claim 2 is drawn to the general formula and specific types of the block copolymer, the cationic surfactant, claim 5 is drawn to the mixing step being performed at a temperature of about -2-8°C; claim 8 is drawn to the block copolymer being CRL-1008; claim 9 is drawn to specific cationic surfactants; claim 10 is to the mixture comprising an amorphous cryoprotectant. Claim 11 is drawn the amorphous cryoprotectant being sucrose; claim 12 is drawn to the inclusion of a crystalline bulking agent; claim 13 is dawn to mixture having 1% to 20% of a crystalline bulking agent; claim 15 is drawn to the mixture comprising a pH stabilizing buffer; claims 16-19 are drawn to the physiologic buffer and concentration amounts. Claim 20 is drawn to the concentration of the cationic surfactant; claim 21 is drawn to the concentration of the block copolymer; claim 22 is drawn to the concentration of the polynucleotides; claims 23-24 are drawn to the product of claim 1; claims 27-28 are drawn to the product of claim 15; claim 29 is drawn to the cationic surfactant being benethonium chloride. Claim 30 is drawn to the cationic surfactant being cetramide; claim 31 is drawn to the cationic surfactant being cetylpyridinium chloride; and claim 32 is drawn to the cationic surfactant being cetyl triethyiammonium chloride. Claims 37-39 are drawn to the compound being a monosaccharide and the produced product. Claims 40-42 are drawn to the compound being a disaccharide and the produced product. Claims 43-45 are drawn to the compound being an oligosaccharide and the produced product.

Evans teach the preparation of compositions comprising a polynucleotide, nonionic block copolymers such as polyoxyethylene (POE)/polyoxypropylene (POP) and a cationic surfactant (POP) at a temperature below the cloud point of said block copolymer to form a mixture (page 3, lines 5-8 and 31-34 and page 32, lines 23-34). Evans states that stabilized vaccines and alternative formulations, including lyophilized formulation have been taught by the incorporated WO 97/40839 reference (page 31, lines 15-18). Evans teaches the Preparation of CRL-1005 (block copolymer) formulations containing DNA and the cationic surfactant by mixing or vortexing the components at temperatures below the cloud point of the polymer, approximately 6-7°C (page 32, lines 23-34). Evans teaches mixing the components at temperatures below the cloud point and within the recited range of claim 5. Evans recites the general POE/POP formula: $HO(C_2H_4O)_a(C_3H_60)_b(C_2H_40)_a$ H, wherein (b) represents a number such that the molecular weight of the hydrophobic POP portion (C_3H_60) is less than 20,000 daltons and wherein (a) represents a number such that the percentage of hydrophilic POE portion (C_2H_4O) is between approximately 1% and 40% by weight (page 4, lines 10-17). Therefore Evans teaches the block copolymers having the general formula and ranges recited by Claim 2. Evans discloses surface-active block copolymer represented by CRL-005 (page 13, lines 19-21), as recited by claim 8.

Evan teaches polynucleotide formulations comprising a cationic surfactant along with the block copolymer (page 13, lines 22-26). Evan teaches the cationic surfactants not limited to: benzalkonium chloride (BAK), benzethonium chloride, cetramide (which contains tetradecyltrimethylammonium bromide, dedecyltrimethylammonium bromide

hexadecyltrimethyl ammonium bromide, cetylpyridinium chloride and cetyl trimethylammonium chloride (page 13, lines 26-34). Thus, Evans teaches the cationic surfactants of claims 9 and 29-31. The composition comprises other excipients, such as glycerol (page 23, lines 10-14). Evans teaches the inclusion of glycerol, an amorphous cryoprotectant, as defined by the specification at paragraph [0079]. The vaccines include a saline solution such as phosphate buffered saline (PBS) (page 30, lines 18-20). The physiologically acceptable buffer in Figure 3 shows the use of 10mM sodium phosphate buffer (page 13, lines 5-27). Thus Evan teaches sodium phosphate buffer within the range of about 5mM to about 25mM, as recited by claims 15-19.

Evans teaches the concentration range of the respective polynucleotide be from about 0.5 mg/ml to about 7.5 mg/ml, the POE and POP block copolymer be at a concentration of from about 1 to about 70 mg/ml and that the cationic surfactant be at a concentration of 0.1 to 10mM (pages 21-22, lines 32-1). Therefore Evan discloses the concentrations of the cationic surfactant at about 0.1 to 5mM, the block copolymer at about 1 to about 50 mg/ml and the polynucleotide at about 1 mg/ml to about 50 mg/ml, from claims 20-22 are disclosed. Evans teaches the formulation was stored at –70C and then allowed to thaw to room temperature (page 33, lines 8-9). Evans teaches providing formulations that provide for long-term stability of the vaccines (page 30, lines 22-23). However Evans do not teach a method of product further comprising a disaccharide compound.

Volkin et al., teach lyophilized DNA formulation comprising amorphous disaccharide sugars, explicitly sucrose and lactose greatly stabilize the DNA (page 81,

lines 11-13). Figure 12 shows lyophilized DNA formulations containing lactose or sucrose and PBS (page 15, lines 27-30). The formulation also comprises 4-5% mannitol (page 15, lines 25-31). Volkin et al., teach methods of preparations and compositions drawn to the compound being a monosaccharide, disaccharide or oligosaccharide and the produced products. Volkin et al., teach the inclusion of mannitol, a crystalline bulking agent, as defined by the specification at paragraph [0081]. Thus, Volkin et al., teach a mixture having 1% to 20% of a crystalline bulking agent. Volkin et al., teach lyophilization allows for greater DNA stability and effectively stabilizes DNA vaccines (page 81, lines 7-11). Volkin et al., teach that during storage DNA vaccines undergo accelerated physiochemical changes, thus Volkin et al., teach formulations to optimize the stability of the DNA (page 9, lines 9-25). Volkin et al., also teach the lyophilization of DNA formulation enhances DNA stability, by reducing molecular motion, and formulations that provide the highest stability include buffers, glycerol and high DNA concentrations (page 11-12, lines 28-5).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply lyophilized polynucleotide formulations comprising disaccharide compounds and crystalline bulking agents as taught by Volkin et al., to Evans method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture in order to optimize the stability of the polynucleotide and provide stable long term polynucleotide formulations. One of

ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because both Evans and Volkin et al., teach the desirability of providing stable polynucleotide vaccines achieved by the specific formulations of Evans and Volkin et al., since Volkin et al., teach that disaccharide sugars such as sucrose and lactose greatly increase stabilization of lyophilized polynucleotide formulations. Furthermore, no more than routine skill would have been required to incorporate formulations that provides the highest stability by including buffers, glycerol and high polynucleotide concentrations as taught by Evans, since Volkin et al., teach the it is well known that these ingredients have the benefit of providing the highest polynucleotide stability. Finally it would have been prima facie obvious to combine the invention of Evans and Volkin et al., to advantageously achieve decreased physiochemical changes of the polynucleotides formulations during their storage.

6. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) further in view of Balasubramaniam (US Patent 5,824,322).

The claims are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; and the other recited components wherein the block copolymer has the general formula recited by Claim 3.

The teachings and suggestions of Evans and Volkin et al., have been set forth above. In addition, Evans teaches the use of POE-POP-POE copolymers such as CRL-

1005 and the use of PLURONIC™ copolymers, which have the general organization POP-POE-POP (page 22, line 20). However Evans did not teach a POP-POE-POP copolymer wherein POP accounted for up to 20,000 daltons of the mass of the copolymer and POE represented between 1% and 50% of the copolymer by weight.

Balasubramaniam teaches compositions containing biologically-active copolymer comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene having the formula: $HO(C_3H_60)_b(C_2H_4O)_a(C_3H_60)_bH$, wherein (b) represents a number such that the molecular weight of the hydrophobe POP $(C_3H_60)_b$ that is between approximately 2,000 and 10,000 daltons and (a) represents a number such that the percentage of hydrophilic POE (C_2H_4O) is between approximately 2% and 30% by weight (col. 13, lines 25-37). These compositions have many beneficial properties including but not limited to reducing enteric microorganisms in the gut of humans and animals (col. 17-18, lines 65-2), interfering with the adherence of microbiological organisms to surfaces (col. 18, lines 18-20), and preventing initiation of disease states and inhibiting transference of organisms (col. 18-19, lines 65-5). The preparations contain a saline solution such as physiologic phosphate buffered saline (PBS) or other physiologic salt solutions (col. 21, lines 17-20). Furthermore, Balasubramaniam teach formulations that are presented and stored in freeze-dried (lyophilized) conditions only requiring the addition of sterile water prior to use (col. 24, lines 60-64).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply compositions containing biologically-active copolymer comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene as taught by

Balasubramaniam to Evans and Volkin et al's method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture in order to reducing enteric microoganisms in the gut of humans and animals. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because Evans, Volkin et al., and Balasubramaniam teach the desirability of providing preparations containing physiologic phosphate buffered saline and freeze-dried (lyophilized) formulations. Furthermore, no more than routine skill would have been required to exchange and use a functionally equivalent block copolymer in the method for preparing a lyophilized composition when Evans and Volkin et al., teach its advantageous properties. Finally it would have been prima facie obvious to combine the invention of Evans, Volkin et al., and Balasubramaniam to advantageously achieve the beneficial properties such as interfering with the adherence of microbiological organisms to surfaces, preventing initiation of disease states and inhibiting transference of organisms with compositions comprising the block copolymers.

7. Claims 4, 6-7 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) in view of Hunter et al., (US Patent 5,811,088).

Claims 4 and 6-7 are drawn to a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; and the other recited components wherein the method further comprises a cold filtration step at a temperature of about –2 to 8°C using a filter. Claims 25-26 are drawn to a stable, monodispersed product produced by the method of claim 4.

The teachings of Evans and Volkin et al., have been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic surfactants. However neither Evans nor Volkin et al., teach a cold filtration step.

Hunter et al., teach cold filtration preparation and solubilization of copolymers in an ice-cold phosphate buffered saline (col. 18, lines 41-43). The cold solution was filter sterilized on 0.22um filters and stored at 4°C (col. 18, lines 43-45). Therefore, Hunter et al., the cold filtration step performed using a filter with a pore size of about 0.01 microns to 2 microns. Hunter et al., teach compositions comprising a surface active copolymer having the general formula $HO(C_2H_4O)_b(C_3H_60)_a(C_2H_40)_bH$, wherein (a) represents an integer such that the hydrophobe represented y (C_3H_60) has a molecular weight of about 1,200 to about 15,000 daltons and wherein (b) represents an integer such that the hydrophile portion represented by (C_2H_4O) constitutes approximately 1% and 50% by weight of the compound being prepared (col. 5, lines 1-17). Hunter et al., teach the composition comprising surfactants also (col. 8, lines 60-63).

Thus Evans, Volkin and Hunter teach a composition comprising a POE and POP block copolymer; a polynucleotide; a cationic surfactant; and an amorphous

cryoprotectant or a crystalline bulking agent produced with a cold filtration step as claimed by claims 4, 6-7 and 25-26.

Therefore it would have been prima facie obvious at the time of applicants' invention to apply lyophilized polynucleotide formulations comprising a cold filtration step as taught by Hunter et al., to method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture as taught by Evans and Volkin et al., in order to provide sterile block copolymer formulations. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because both Evans and Volkin et al., teach the desirability of providing formulations containing block copolymers at a temperature at which they are soluble, i.e., below their cloud point, and Hunter et al., teach cold filtration of those same soluble block copolymers in an ice-cold phosphate buffered saline. Furthermore, no more than routine skill would have been required to incorporate the method and formulations as taught by Hunter et al., in the method and formulation of Evans and Volkin et al., since Hunter et al., teach saving time and materials to sterilize the compositions after they have been mixed and rather than separately and individually treat the components. Finally it would have been prima facie obvious to combine the invention of Evans, Volkin et al., and Hunter et al., to advantageously achieve produce a stable, monodispersed product produced by the cold

filter method, since the prior art teaches that such techniques are well known to create sterile compositions.

8. Claims 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) in view of Munsunuri et al., (WO 99/21591).

Claim 11 is drawn the amorphous cryoprotectant being sucrose; claim 12 is drawn to the inclusion of a crystalline bulking agent; claim 13 is dawn to mixture having 1% to 20% of a crystalline bulking agent; and claim 14 is drawn to the final concentration of sucrose being 10%.

The teachings of Evans and Volkin et al., have been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic surfactants. However Evans and Volkin et al., do not teach mixing sucrose as the cryoprotectant at a concentration of 10%.

Munsunuri et al., teach sucrose being present in a polynucleotide admixture in a concentration of about 0 to about 9.25% w/v, or concentrations greater than 9%w/v wherein one skilled in the art of pharmaceutical preparations could readily adjust this characteristic of the complex (page 13, lines 8-12). Munsunuri et al., teach composition comprising soluble ionic complexes comprising a surfactant and a polynucleic acid sequence (page 4, lines 1-5). Munsunuri et al., teach compositions containing aqueous buffers, like phosphate buffered saline for use in forming the complexes in concentrations at about 2 to about 50 mM (page 12, lines 19-29). Thus Munsunuri et al.,

teach the use of physiologic buffers in the mixture within the instantly recited ranges. Munsunuri et al., teach compositions that include sucrose, mannitol, sorbitol and trehalose (page 13, lines 4-8). Example 1 of Munsunuri et al., shows the mixing of compositions comprising the surfactant, the polynucleic acid sequences, a phosphate buffer, tonicity agents such as sucrose, mannitol, trehalose or any other non-ionic agent (page 30, lines 13-21). It is noted that the instant specification, at pages 22-23, names sucrose and sorbitol as amorphous cryoprotectants and mannitol and trehalose and crystalline bulking agents, thus Munsunuri et al., teach the instantly recited agents used within the instantly claimed ranges. Example 1 also shows filtering the admixtures using a commercially obtained 0.22um filter.

Therefore it would have been prima facie obvious at the time of applicants' invention to include concentrations of sucrose at about 10%w/v as taught by Munsunuri et al., in the method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture as taught by Evans and Volkin et al., in order to optimize the stability of the polynucleotide and provide stable long term polynucleotide formulations in order to adjust and achieve desirable tonicity in the compositions. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because Evans, Volkin et al., and Munsunuri et al., already teach sugars such as sucrose will greatly stabilize lyophilized polynucleotide formulations. No more than routine skill would have been

required to incorporate sucrose within the polynucleotide method of preparation and compositions because Evans and Volkin et al., already teach a method of lyophilizing polynucleotides and surfactants in a composition wherein the composition include sucrose. Furthermore, the limitations drawn to the different concentrations for sucrose are viewed as merely optimizing the experimental parameters and not imparting patentability; thus no more than routine skill would have been required to change the concentration in the well known compositions and method of production as taught by Evans, Volkin et al., and Munsunuri et al.

9. Claims 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans (WO 02/00844) and Volkin et al., (WO 97/408839) in view of Felgner et al., (US Patent 5,459,127).

Claim 33 is drawn to the cationic surfactant being (±)-N-(Benzyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminium bromide(Bn-DHxRIE); Claim 34 is drawn to the cationic surfactant being (±)-N-(2-Acetoxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (DHxRIE-OAc); Claim 35 is drawn to the cationic surfactant being (±)-N-(2-Benzoyloxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminiurn bromide (DHxRIE-OBz); and Claim 36 is drawn to the cationic surfactant being (±)-N-(3-Acetoxypropyl)-N,N-dirnethyl-2,3-bis(octyloxy)-l-propanaminium chloride (Pr-DOctRIE-OAc).

The teachings of Evans and Volkin et al., have been set forth above and render obvious methods of mixing polynucleotides with POE-POP copolymers and cationic

surfactants. However Evans and Volkin et al., do not teach the specifically above recited cationic surfactants.

Felgner et al., teach examples of useful cationic lipids to include (+)-N-(Benzyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminium bromide(Bn-DHxRIE), (±)-N-(2-Acetoxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (DHxRIE-OAc), (±)-N-(2-Benzoyloxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-l-propanaminiurn bromide (DHxRIE-OBz), (±)-N-(3-Acetoxypropyl)-N,N-dirnethyl-2,3-bis(octyloxy)-l-propanaminium chloride (Pr-DOctRIE-OAc). Felgner et al., teach these cationic lipids all have the same general structure (col. 4, lines 56-64). These cationic lipids are suitable for intracellular delivery of polynucleotides (col. 4, lines 50-55). The cationic lipids further comprise cationic groups that enhance the effectiveness of the lipids in interacting with the cell membrane (col. 8-9, lines 65-1). The lipid formulations are amenable to freeze-dry techniques (col. 15, lines 23-26).

Therefore it would have been prima facie obvious at the time of applicants' invention to include the cationic surfactants of claims 33-36 as taught by Felgner et al., in the method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; (ii) a polynucleotide; (iii) a cationic surfactant; at a temperature below the cloud point of said block copolymer to form a mixture; and (b) lyophilizing the mixture as taught by Evans and Volkin et al., in order to effectively deliver polynucleotides formulations intracellularly. One of ordinary skill in the art would have a reasonable expectation of success by modifying the method of preparation because Evans and Volkin et al.,

already teach cationic lipid surfactants incorporated with methods of preparation and compositions comprising block copolymers, polynucleotides, cationic surfactants and compounds. No more than routine skill would have been required to incorporate the cationic surfactants of claims 33-36 as taught by Felgner et al., into the methods and compositions of Evans and Volkin et al., because Felgner et al., teach that surfactants as enhancing the effectiveness of the lipids in interacting with the cell membrane. Furthermore, no more than routine skill would have been required to exchange and use a functionally equivalent block copolymer in the method for preparing a lyophilized composition when Evans, Volkin et al., and Felgner et al., teach its advantageous use with lyophilized polynucleotide compositions.

Conclusion

10. No claims allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
May 7, 2007

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER